A Multivariate Twin Study of Female Sexual Dysfunction

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ABSTRACT

Introduction. There is little work on the etiology of female sexual dysfunction (FSD), a highly contentious and heterogeneous disorder from classification and clinical perspectives. Clarifying causative mechanisms may enhance current psychiatric nosology.

Aim. To elucidate the structure of genetic and environmental risk factors underlying the major subtypes of FSD.

Methods. Self-report questionnaires and multivariate twin model fitting on a population-based adult twin register (TwinsUK, London) including 1,489 female twins aged 18 to 85, comprising 244 MZ pairs, 189 DZ pairs, and 623 women whose co-twins did not participate.

Main Outcome Measures. Scores on the Female Sexual Function Index–Lifelong and its six dimensions (desire, arousal, lubrication, orgasm, satisfaction, and pain) were subject to univariate and multivariate variance component analysis.

Results. The best-fitting multivariate model was an ACE Cholesky model, in which both additive genetic effects and non-shared environmental effects loaded on four FSD dimensions. There was significant genetic sharing between desire, arousal, lubrication and orgasm, but there was also significant genetic sharing between arousal, lubrication and orgasm independent of desire. These genetic loadings were small to modest effects (7% to 33%). Bivariate heritabilities suggested that a third of the covariance between these dimensions was genetic. Desire shared the least amount of genetic association with lubrication and orgasm. Non-shared environmental effects (which were stronger than genetic effects) were somewhat more dimension-specific.

Conclusions. FSD is not etiologically homogeneous. There are at least two genetic factors to FSD symptomatology, and a tendency for more dimension-specific non-shared environmental factors as a more important indicative of unique factors involved in specific types of sexual problems reported by women. These results emphasize genetic factors as possible organizing principles for an etiologically based classification approach of FSD. Burri A, Greven C, Leupin M, Spector T, and Rahman Q. A multivariate twin study of female sexual dysfunction. J Sex Med **,**:–**.

Key Words. FSFI; Female Sexual Dysfunction; Genetic; Heritability; Multivariate

Introduction

Female sexual dysfunction (FSD) is a broad term encompassing disorders of sexual desire, arousal, orgasm, and sexual-activity-related pain. It appears relatively common in general community settings (up to 40% of adult women report at least one dysfunction) and severely impacts women’s quality of life [1–3]. However, the diversity of FSD-related disorders suggests positing a single diagnostic entity is over-simplistic and has drawn heavy criticism from scholars across disciplines. Moreover, the etiology of FSD-related constructs is largely unknown although researchers have proposed biological and psychological factors [4]. This lack of knowledge has hampered
progress in both psychiatric nosology and treatment strategies for this critical aspect of women’s mental health. Both DSM-IV and International Classification of Diseases, Tenth Revision have arranged FSD into categories based largely on clinical similarities, while in 1998 a consensus-based definition and classification system was designed by the International Consensus Development Conference [1,5].

Preliminary basic research findings as well as observations from clinical practice have challenged several features of the current classification system (DSM-IV-TR), especially in view of the deliberations regarding DSM-IV gender identity and sexual disorders categories [6–11]. For example, the current requirement of sexual distress as the primary diagnostic criterion is not supported by epidemiological studies. These show that sexual problems, independent of degree of severity, do not always cause distress. Shifren et al. reported that the prevalence of low sexual arousal decreased from 25.3% to approximately 6% when including distress [12], whereas Dennerstein & Hayes observed that 16% of women aged 20–49 years had low sexual desire compared with only 7% when personal distress was included as a diagnostic criterion [13]. For a comparison of classification problems for ICD-10 diagnosis of FSD, see King et al. [14]. Moreover, there is burgeoning evidence for a separation of sexual desire and arousal and the division of arousal into subjective and genital arousal [6,15]. Several pieces of psychophysiological evidence suggest that women’s self-reported, subjective arousal does not necessarily correlate with the levels of their genital response [16–18]. A meta-analysis by Chivers et al. quantified the degree of agreement between self-reported and genital measures of sexual arousal and reported low agreement between the two measures ($r = 0.26$) [16]. The authors proposed that moderating variables such as stimulus variability and timing of the assessment of self-reported sexual arousal may explain the poor correlation. Moreover, neuroimaging studies report that the magnitude of hypothalamic activation (an area of the brain known to play a crucial role in physiological sexual arousal, sexual preferences and behavior) is less correlated with self-reported levels of sexual arousal in women than it was in men [18]. A large body of quantitative psychophysiological evidence using vaginal photoplethysmographic amplitude (VPA) also shows that a VPA response occurs to sexual stimuli, but subjective sexual arousal remains low or non-existent [17].

These studies suggest that part of the confusion surrounding FSD arises from symptom heterogeneity. This heterogeneity may be due to overlapping or partially overlapping etiological mechanisms. For example, if one set of etiologies explains most FSD-type reported problems, then conceptualizing FSD as possessing a relatively unitary underlying structure may benefit diagnosticians, researchers, and mental health professionals. Alternatively, FSD might be associated with common and unique etiologies (some causative factors may be common to all FSD symptoms and others unique to specific symptoms), which may support the burgeoning multidimensional approach to definition, classification, and treatment. The structure of these putative etiological pathways has yet to be tested.

Several factors unique to specific FSD symptoms have indeed been identified in cross-sectional and epidemiological-level studies (including anxiety, depression, and personality risk factors) and many of these factors have a strong heritable basis as tested by twin models [19–21]. Only one twin study has quantified the genetic contribution to FSD symptoms suggesting that both genetic and environmental factors may contribute [22]. However, genetic effects in this study were small, 0% to 15%, and the remaining proportion of the variance was entirely due to individual-specific environmental factors, so called non-shared environments, and measurement error. Two other studies, not directly testing FSD, found modest genetic influences (20% to 45%) on orgasm frequency, depending on whether orgasm was measured during sexual intercourse or other sexual activity [23,24]. The difference in the size of the genetic contributions to orgasm between these studies requires further testing. These studies are also somewhat limited by their use of measures that do not capture lifetime reporting of FSD symptoms. A lifetime-reporting measure of Female Sexual Function Index (FSFI) may offer better characterization of the FSD phenotype because lifetime sexual function is more enduring compared to the oft-used 4-week reporting measure (which, while capturing short-term variation in sexual responses, may be overly sensitive to idiosyncratic contextual and environmental effects). These shortcomings limit the interpretation of the data in these studies about the putative underlying structure of variations in sexual problems reported by women [25]. Variation between twin studies in genetic estimates may in part be due to poor phenotypic
characterization so here we opted for using the lifetime FSFI.

Here, we aim to clarify the etiological structure underlying FSD by dissecting the covariation between FSD dimensions (desire, subjective arousal, genital arousal, and orgasm) into genetic and environmental components based on a large sample of unselected female twins from the general population. This will provide a comprehensive picture of the structure of genetic and environmental risk factors underlying the FSD dimensions and their associations. Based on the previous epidemiological, cross-sectional, clinical, and twin findings, we predicted that the phenotypic covariation between FSD dimensions would be influenced by common as well as specific factors (genetic and non-shared environmental ones). We also predicted that the influence of shared environmental factors (defined as environments that contribute to similarities between siblings from the same family) would be negligible. Exploring the utility of multivariate twin models to parse out the multidimensional nature of FSD will encourage other researchers to use them to enhance our understanding of the underlying etiological structure of other complex psychiatric disorders.

Methods

Participants
Participants were MZ and DZ female twins enlisted in the TwinsUK registry [26]. The UK Adult Twin Registry is a cohort of unselected volunteer Caucasian twins that started in 1993. All volunteers in the registry have been recruited through successive national media campaigns in the United Kingdom and Ireland and from other twin registers. The TwinsUK population is comparable to age-matched British population singletons in terms of disease prevalence, demographic, and lifestyle characteristics [27]. Zygosity has been confirmed via standard questionnaires and, in cases of uncertainty, confirmed by multiplex DNA genotyping [28,29]. Moreover, the twin cohort has been shown to be representative of the general population for a wide range of sexual lifestyles and sexual behaviors [30,31]. The project was approved by the St. Thomas’ Hospital Research Ethics Committee, and all twins provided informed consent. The twins were unaware of the research hypotheses addressed here.

Collection of responses to the FSFI-Lifelong (FSFI-LL) was carried out in 2008/2009 [31]. This questionnaire was sent to a subsample of 3,175 twin individuals (mean age, 56.2; SD, 12.1; range, 25–85 years) who had previously completed sexuality measures and had stated their willingness to participate in further surveys of this nature; 1,589 women returned the questionnaire (response rate, 50%). For reason of standardization, 19 (1.3%) women reporting being homosexual were also omitted. Those with more than 5 of the 19 items in the FSFI and FSFI-LL and/or more than two items of the FSDS missing were further dropped from the sample (72 [4.8%]). To maximize the number of twin pairs available for analyses—in cases where subjects had ≤5 of the 19 items in the FSFI-LL missing—missing values (N = 72) were imputed with item-specific means of the non-missing values, separately calculated for four different age groups: 18–30, 31–45, 46–55, and 56–85 years. This method of dealing with missing value has been used before in genetic epidemiologic studies investigating FSD [22]. After applying exclusion criteria and imputation, a total of 1,489 women were eligible for analyses, comprising 244 full MZ pairs, 189 full DZ pairs, and 623 women whose co-twins did not participate (41.8%).

Measures

The 19-item FSFI-LL is a self-report questionnaire recently developed to measure long-term variation in female sexuality, including periods of dysfunction and healthy function [31,32]. For genetic analysis, the FSFI-LL is preferable to the often used FSFI which records FSD symptoms experienced during the 4 weeks before presentation and, therefore, focuses on short-term sexual functioning only [32]. Short-term sexual responses in women are affected by myriad situational factors. Thus, the “snapshot” approach of the FSFI poorly captures the variation in enduring female sexual functioning required for resolving the underlying genetic and non-genetic structure of FSD symptoms. The FSFI-LL assesses six dimensions of women’s average sexual functioning since they have been sexually active including desire (two items), arousal (four items), lubrication (four items), orgasm (three items), satisfaction (three items), and pain (three items). Response options to each question are on a Likert-type scale ranging from 1 to 5 for items 1 and 2. For all other items (3–19), the range is from 0 to 5 with the supplementary option “no sexual activity.” Dimension scores are derived by summing the item scores within each dimension and multiplying the sum by the specific dimension factor weight [32].
dimension factor weighing converts the dimension scores to a consistent range from 0 to 6, except for the desire, which has a dimension score range from 1.2 to 6. Total scores are calculated via a simple computational algorithm [32]. Low scores on the FSFI-LL indicate more sexual problems and high scores indicate fewer problems.

The FSFI-LL has excellent psychometric properties for both total- and dimension-specific scores, including test–retest reliability, internal consistency, and external and discriminant validity [31,32]. Internal consistencies (Cronbach α) range from 0.76 to 0.92. Exploratory and confirmatory factor analyses have successfully reproduced the original six-factor structure, hence supporting the construct validity of the measure [31]. A cut-off score of 26.55 is used to discriminate “dysfunction” (in those classed as patients) from healthy function. According to response operator curve (ROC)-derived cut-off scores, all dimensions and the total FSD score displayed a good sensitivity to 1-specificity profile (as measured by the area under the curve = AUC), with arousal (AUC = 0.92) displaying the best trade-off and desire the lowest (AUC = 67.55%). Overall, the FSFI-LL demonstrates excellent comparability to the standard FSFI in terms of factor structure and psychometric properties [31]. Here, all dimensions of the FSFI-LL were handled as continuous phenotypes.

### Data Analysis and Genetic Modeling

Data handling and analyses concerning means, variances, and twin (intra-class) correlations were conducted with STATA (version 10, StataCorp, College Station, TX, USA) and the structural equation modeling package Mx [33]. Unpaired two-tailed t-tests were used to test mean differences in age and FSFI-LL scores between MZ and DZ twins (the non-independence of data here was controlled for using the cluster command in STATA, see Table 1). Because of the skewness of the distributions, all phenotypes, except desire and arousal were either log- or square-root transformed. Genetic modeling analyses were also conducted with Mx [33]. Because the perfect correlation for age within twin pairs can bias parameters estimates [34], and because of the frequently reported age-dependency of FSD, standard corrections for age were applied by means of regression prior to genetic modeling. We used full-information maximum likelihood estimation (FIML) because this approach allows the inclusion of missing data, while minimizing any potential bias introduced by doing so [35].

#### Univariate Genetic Modeling

Genetic model fitting analysis was used to dissect the observed phenotypic variance (P) of FSFI-LL scores into additive genetic (A), dominant genetic (D), common environmental (C) and unique environmental (E) components [36]. In the standard twin model, C and D cannot be simultaneously estimated for reasons of model identification so twin correlations were used to give initial indications of whether C or D effects were present (e.g., DZ within-pair correlations less than half the MZ within-pair correlations would provide initial evidence for dominant genetic influences). These indications were then formally quantified in the model fitting analyses. Significance of parameters (A, D, C, and E) can be evaluated using 95% confidence intervals and then assessed by sequentially removing parameters (except E, which includes measurement error) from the full model and testing the deterioration in fit. The goodness of fit of the genetic models was evaluated by comparing them with an unconstrained saturated model, which estimates the maximum number of parameters without partitioning variance into genetic and environmental components. This gives rise to a likelihood ratio chi-square tests

<table>
<thead>
<tr>
<th>Overall (N = 1,489)</th>
<th>MZ (N = 757)</th>
<th>DZ (N = 732)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td><strong>Desire</strong></td>
<td><strong>Arousal</strong></td>
</tr>
<tr>
<td>Mean 56.30</td>
<td>Mean 3.77</td>
<td>Mean 4.36</td>
</tr>
<tr>
<td>SD 11.63</td>
<td>SD 0.88</td>
<td>SD 0.97</td>
</tr>
<tr>
<td>Range 18–85</td>
<td>Range 1.2–6</td>
<td>Range 1.2–6</td>
</tr>
<tr>
<td><strong>Lubrication</strong></td>
<td><strong>Orgasm</strong></td>
<td><strong>Satisfaction</strong></td>
</tr>
<tr>
<td>Mean 5.04</td>
<td>Mean 4.53</td>
<td>Mean 4.70</td>
</tr>
<tr>
<td>SD 0.89</td>
<td>SD 1.22</td>
<td>SD 1.20</td>
</tr>
<tr>
<td>Range 1.2–6</td>
<td>Range 1.2–6</td>
<td>Range 1.2–6</td>
</tr>
<tr>
<td><strong>Pain</strong></td>
<td><strong>Total FSD</strong></td>
<td></td>
</tr>
<tr>
<td>Mean 5.28</td>
<td>Mean 27.70</td>
<td></td>
</tr>
<tr>
<td>SD 0.82</td>
<td>SD 4.42</td>
<td></td>
</tr>
<tr>
<td>Range 1.2–6</td>
<td>Range 8.2–36</td>
<td></td>
</tr>
</tbody>
</table>

Note. SD = Standard Deviation. P values refer to unpaired t-tests, which compare means for monozygotic (MZ) and dizygotic (Dz) twins.

Table 1 Mean age and FSFI-LL scores for the overall sample (N = 1,489) and by zygosity.
(-2LL; significant tests indicate significant deterioration in fit) and Akaike's Information Criterion (AIC; a parsimony fit index, with lower values indicating the more suitable model); [37]. We chose the best-fitting models on the basis of parsimony.

**Multivariate Genetic Modeling**

Multivariate analyses were used to decompose the covariation of FSD dimensions into genetic and environmental factors. Cross-twin cross-trait correlations can be used to obtain an initial impression of genetic and environmental contributions to covariation. Greater cross-twin cross-trait correlations in MZ compared to DZ twins indicate that genetic factors contribute to the phenotypic correlation between traits. If the DZ cross-twin cross-trait correlations are more than half the MZ cross-twin cross-trait correlations, shared environmental influences are implicated. In cases where the DZ correlations are less than half the MZ correlations, dominant genetic effects are implicated. Any deviation of MZ cross-twin cross-trait correlations from the phenotypic correlations implicates non-shared environmental influences in the covariation. Included in the multivariate analyses were the dimensions of desire, arousal, lubrication, and orgasm because phenotypic correlations were highest between these dimensions, suggesting that common factors may underlie these traits. Satisfaction and pain showed lower inter-correlations and were, therefore, not included in the analyses.

To formally quantify the genetic and environmental structure behind the covariation between the FSD dimensions, the data were fitted to three multivariate models that were compared to an unconstrained saturated model. The three models were the Cholesky decomposition, the independent pathway, and the common pathway model. The Cholesky decomposition provides the correlations between the four independent genetic and environmental factors (A, C, D, E) and decomposes the variance of our phenotypes into distinct additive genetic and distinct non-shared environmental effects, providing the fullest potential explanation of the data. The expected variance-covariance matrix is parameterized in terms of N (number of variables) latent factors. In other words, all the genetic variation in, e.g., desire is associated with factor A1, whereas factor A2 represents genetic influences shared between arousal, lubrication, and orgasm independent of genetic influences shared with desire. Thus, A2 can be seen to summarize residual genetic effects after accounting for the first general genetic factor [38].

The independent pathway model is a submodel of the Cholesky model. It tests whether the covariance between desire, arousal, lubrication, and orgasm can be explained by a single shared genetic and shared environmental factor. An independent pathway model would suggest that all phenotypes share common etiological factors that could lead to some kind of predisposition to FSD. A common pathway model suggests that a latent phenotype, like for example personality or anxiety, underlies FSD, which, in turn, is influenced by shared genetic and shared unique environmental factors. To determine goodness of fit likelihood chi-square tests and the AIC were used.

**Results**

Characteristics of the overall sample (N = 1,489) and comparisons by zygosity are shown in Table 1. The mean age of participants in the study was 56.3 years (Standard Deviation [SD] 11.63; range 18–85 years). No significant differences between MZ and DZ twins in age and FSFI-LL scores could be detected. This suggests that the MZ and DZ twin groups were well matched for age and all dimensions of the FSFI-LL (Table 1). In addition, FSFI dimension scores and age were compared between women with full data available and women whose missing values have been imputed (Table 2). While there was a significant difference in age between the two groups, no other significant differences in sexual functioning could be detected.

**Univariate Model Fitting**

As MZ twin correlations were larger than twice the DZ correlations, genetic effects were implicated in each FSD dimension (Table 3). As MZ twin correlations deviated substantially from unity, non-shared environmental influences (including measurement error) were also implicated. Univariate model fitting analysis confirmed the presence of a genetic influence on each FSFI-LL dimension. The best fitting model for all dimensions contained only additive genetic and non-shared environmental components (the AE model). Influences of C or D were non-significant. Parameter estimates derived from the AE models are shown in Table 3. Consistent with the twin correlations, additive genetic effects were moderate for all dimensions, explaining 22% (for sexual satisfaction) to 39% (for overall FSD) of the variance, whereas non-shared environmental factors accounted for the remaining 61% (for overall
FSD) to 78% (for sexual satisfaction). The confidence intervals were relatively narrow across all phenotypes indicating good precision of our point estimates.

Multivariate Model Fitting

Cross-twin cross-trait correlations deviated notably from phenotypic correlations and were consistently higher in MZ than DZ twins, indicating genetic and non-shared environmental influence on covariation. We fitted ACE and ADE models to our data; however, we only present ACE models, which provided superior fit in all instances.

The results of the multivariate model-fitting analysis showed that the AIC index of parsimony favors the Cholesky model with a Δ-2LL of 113.6 at 62 df and lowest ΔAIC of 5.6 compared to the independent pathway model (Δ-2LL of 145.9 at 60 df and lowest ΔAIC of 9.9) and the common pathway model (Δ-2LL of 191.2 at 68 and lowest ΔAIC of 43.2) (Table 4). In the Cholesky model, the expected variance–covariance matrix is parameterized in terms of N latent factors. For example, all the genetic variation in the desire dimension is associated with factor A1 but the remaining paths (drawn in Figure 1) from A1 to arousal, lubrication and orgasm indicate that this factor is also shared by these dimensions. A2 represents genetic influences shared between arousal, lubrication, and orgasm, but independently of any genetic effects shared with desire.

Genetic and environmental correlations derived from the ACE Cholesky model are shown in Table 5, along with the phenotypic correlations for all FSD dimensions. The genetic correlations suggested that arousal is highly correlated genetically with desire ($r_A = 0.86$), but also with lubrication ($r_A = 0.90$) and orgasm ($r_A = 0.92$), whereas desire is somewhat less correlated with lubrication and orgasm ($r_A = 0.60$ and 0.59, respectively), although genetic correlations were not significantly different as 95% confidence intervals overlapped. The bivariate heritabilities were moderate, ranging from 35% to 44%, suggesting that on average a third of the covariance between the four different traits was due to additive genetic factors with the remaining covariance being largely attributable to non-shared environmental factors (Table 5). Common shared environmental influences on the phenotypic variance and covariance between the four dimensions was negligible.

Figure 1 shows that consistent with the pattern of genetic correlations the best-fitting Cholesky

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**Table 2** Comparison of mean age and FSFI dimension scores in women with full FSFI data available and women with missing (imputed) data

<table>
<thead>
<tr>
<th></th>
<th>Full data (N = 1,417)</th>
<th>Missing data (N = 72)</th>
<th>P value*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
</tr>
<tr>
<td>Age</td>
<td>55.97</td>
<td>11.51</td>
<td>60.50</td>
</tr>
<tr>
<td>Desire</td>
<td>3.79</td>
<td>0.87</td>
<td>3.64</td>
</tr>
<tr>
<td>Arousal</td>
<td>4.39</td>
<td>0.96</td>
<td>4.18</td>
</tr>
<tr>
<td>Lubrication</td>
<td>5.06</td>
<td>0.88</td>
<td>4.86</td>
</tr>
<tr>
<td>Orgasm</td>
<td>4.56</td>
<td>1.22</td>
<td>4.31</td>
</tr>
<tr>
<td>Satisfaction</td>
<td>4.72</td>
<td>1.19</td>
<td>4.54</td>
</tr>
<tr>
<td>Pain</td>
<td>5.25</td>
<td>0.81</td>
<td>5.09</td>
</tr>
<tr>
<td>Total FSD</td>
<td>27.81</td>
<td>4.39</td>
<td>26.87</td>
</tr>
</tbody>
</table>

*P value = ns means non-significant

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**Table 3** Intra-class correlations (R) for MZ (N = 244 full pairs) and DZ twins (N = 189 full pairs), and heritability and non-shared environmental estimates for all domains of the FSFI-LL

<table>
<thead>
<tr>
<th>Phenotype</th>
<th>Persistent FSD</th>
<th>$R_{oz}$ (95% CI)</th>
<th>$R_{dz}$ (95% CI)</th>
<th>% due to A (95%CI)</th>
<th>% due to E (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Desire</td>
<td>0.36 (0.21–0.43)</td>
<td>0.17 (0.02–0.33)</td>
<td>0.35 (0.24–0.44)</td>
<td>0.65 (0.55–0.75)</td>
<td></td>
</tr>
<tr>
<td>Arousal</td>
<td>0.28 (0.18–0.42)</td>
<td>0.13 (0.00–0.30)</td>
<td>0.26 (0.16–0.37)</td>
<td>0.74 (0.62–0.84)</td>
<td></td>
</tr>
<tr>
<td>Lubrication</td>
<td>0.28 (0.21–0.44)</td>
<td>0.11 (0.00–0.19)</td>
<td>0.25 (0.13–0.36)</td>
<td>0.75 (0.63–0.87)</td>
<td></td>
</tr>
<tr>
<td>Orgasm</td>
<td>0.27 (0.26–0.48)</td>
<td>0.10 (0.00–0.19)</td>
<td>0.28 (0.16–0.39)</td>
<td>0.72 (0.60–0.84)</td>
<td></td>
</tr>
<tr>
<td>Satisfaction</td>
<td>0.28 (0.16–0.39)</td>
<td>0.07 (0.00–0.18)</td>
<td>0.22 (0.10–0.33)</td>
<td>0.78 (0.67–0.90)</td>
<td></td>
</tr>
<tr>
<td>Pain</td>
<td>0.34 (0.23–0.45)</td>
<td>0.07 (0.00–0.23)</td>
<td>0.31 (0.20–0.41)</td>
<td>0.69 (0.60–0.94)</td>
<td></td>
</tr>
<tr>
<td>Total FSD</td>
<td>0.41 (0.31–0.51)</td>
<td>0.09 (0.00–0.25)</td>
<td>0.39 (0.28–0.49)</td>
<td>0.61 (0.56–0.68)</td>
<td></td>
</tr>
</tbody>
</table>

Note. % due to A represents the proportion of variance due to additive genetic factors (i.e., the heritability). % due to E represents the proportion of variance due to non-shared environmental factors. CI = confidence interval

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model suggests the existence of two (relatively weak) genetic factors. Genetic factor A1 represented a general genetic factor shared by all phenotypes and accounted for 7% (for lubrication) to 33% (for desire) of the variation. Factor A2 loaded weakly on arousal (7%) and moderately on lubrication (10%) and orgasm (17%). The contribution of environmental factors to the variation of each trait was consistently higher than the contribution of genetic factors, ranging up to 65% for factor E1 (on desire). In sum, four non-shared environmental factors were identified. Although three of the four factors loaded moderately on various domains of sexual functioning (for example, factor E1 showing factor loads of 65% for desire and 17% for arousal), they seemed rather dimension-specific, with, for example, factor E1 loading most strongly on desire (65%), factor E2 loading most strongly on arousal (55%) and factor E3 loading most strongly on lubrication (56%).

Table 4 Results of multivariate modeling for the four subdomains of FSD—desire, arousal, lubrication, and orgasm. Fit indices for the three quadrivariate models—AE Cholesky, independent pathway, and common pathway model—represent the difference in values compared to the unconstrained saturated model.

<table>
<thead>
<tr>
<th></th>
<th>4variate Cholesky</th>
<th>Independent pathway model</th>
<th>Common pathway model</th>
</tr>
</thead>
<tbody>
<tr>
<td>-2LL</td>
<td>113.635</td>
<td>145.883</td>
<td>191.174</td>
</tr>
<tr>
<td>df</td>
<td>62</td>
<td>60</td>
<td>68</td>
</tr>
<tr>
<td>p</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>AIC</td>
<td>5.635</td>
<td>9.883</td>
<td>43.174</td>
</tr>
</tbody>
</table>

Note. -2LL = Likelihood ratio chi-square tests; df = degrees of freedom; p = P value of the chi-square tests; AIC = Akaike information criterion

Table 5 Proportion of phenotypic correlations due to additive genetic (A), shared environmental (C), and non-shared environmental (E) influences; and genetic, shared environmental, and non-shared environmental correlations (95% CI)

<table>
<thead>
<tr>
<th>Correlations</th>
<th>D-AR</th>
<th>D-L</th>
<th>D-O</th>
<th>Ar-L</th>
<th>Ar-O</th>
<th>L-O</th>
</tr>
</thead>
<tbody>
<tr>
<td>r_P</td>
<td>0.60</td>
<td>0.39</td>
<td>0.39</td>
<td>0.58</td>
<td>0.68</td>
<td>0.56</td>
</tr>
</tbody>
</table>

Proportion of r due to:

- A: 0.44 (0.2–0.58)
- C: 0.02 (-0.03–0.37)
- E: 0.56 (0.42–0.70)

Correlations:

- r_A: 0.86 (0.54–1.0)
- r_C: 0.70 (0.59–0.86)
- r_E: 0.48 (0.40–0.56)

Note. r_P = phenotypic correlation; r_A, r_C, r_E = additive genetic, shared environmental and non-shared environmental correlations, respectively. D = desire; Ar = arousal; L = lubrication; O = orgasm

Discussion

FSD is both a phenomenologically contentious diagnostic classification and is marked by substantial phenotypic heterogeneity. Here, we used mul-

Figure 1 Illustration of the Cholesky decomposition for the covariances of sexual problems between desire, arousal, orgasm, and lubrication. The figure shows parameter estimates for the path coefficients of the Cholesky Model AE model, selected as the most appropriate depiction of the data. The phenotypic variance in 244 MZ and 189 DZ twin pairs was decomposed to additive genetic (A1–A4) and non-shared environmental (E1–E4) factors. No common environmental factors (C) could be detected. The path coefficients provide an estimate of the variance of each dimension explained by the influence of additive genetic (A1–A4) and non-shared environmental factors (E1–E4). Standardized factor loadings with 95% CI are displayed.
tivariate twin analysis to clarify the genetic and environmental factors underlying the FSD dimensions and their associations. Our results supported the prediction that the covariation between FSD dimensions (including sexual desire, arousal, lubrication, and orgasm symptoms) would be due to genetic and environmental factors partially shared between the FSD dimensions.

Heritability of FSD Dimensions
The best fitting model from the univariate analyses comprised additive genetic and non-shared environmental factors (including measurement error). The results showed that all FSD dimensions, including overall FSD score, were modestly heritable (22% to 39%). These estimates are comparable to two studies on self-reported orgasm frequency in non-clinical female twins (20–45%) [23,24] but were higher than those reported in one other sample of twins reporting on the 4-week FSFI measure (0–15%) [22]. However, in line with other studies, we found no evidence for environmental influences shared by siblings on individual differences in FSD dimensions [22–24]. Instead, the type of environmental influences that were important were entirely of a non-shared nature and were greater than genetic effects.

Genetic and Environmental Influences on the Covariation between FSD Dimensions
The multivariate genetic analysis revealed moderate to high genetic and non-shared environmental correlations between desire and arousal, arousal and lubrication, arousal and orgasm, and lubrication and orgasm (genetic correlations ranged from 0.86 to 0.94; non-shared environmental correlations ranged from 0.48 to 0.61). This suggests that these FSD dimensions were substantially influenced by the same genes and the same non-shared environments (such as, for example, the same traumatic events). Phenotypic correlations were also highest between these FSD dimensions (range from 0.58 to 0.68). Genetic and non-shared environmental correlations between desire and lubrication and desire and orgasm were somewhat lower (genetic correlations of 0.59 and 0.60; non-shared environmental correlations of 0.31 and 0.32, respectively), and these FSD dimensions also correlated lower phenotypically (0.60 and 0.59). Moreover, the phenotypic associations between the FSD dimensions could largely be attributed to non-shared environments (over 50%), whereas genetic factors explained the remaining proportions of covariance.

In summary, this indicates some etiological heterogeneity to FSD, consistent with the multi-dimensional construct of lifelong FSD deliberated at the 1998 International Consensus Development Conference [1]. This was supported by the finding that a common pathway model (which assumes a common underlying structure to traits with variant dimensions) provided a poor fit to the data, indicating that the different FSD dimensions are not explained by an underlying unitary FSD entity [21]. An independent pathway model also provided a worse fit to the data militating against an argument for single shared genetic and environmental factors loading on each dimension.

These findings point to an etiological distinction between those components of FSD that are predominantly psychological (desire) compared with those that comprise both psychological and physiological mechanisms (arousal), and those with a strong physiological basis (lubrication and orgasm). If these findings were replicated (and with objective as well as self-report measures of arousal, lubrication, and orgasm), they may support the deliberations by the International Consensus Panel to include subjective sexual arousal and genital sexual arousal disorders as possibly separate FSD subtypes [8]. However, we reiterate that replication of the present findings would be important in order to ensure drawing such distinctions are not done prematurely.

Although we found evidence for significant genetic overlap across certain FSD dimensions, the covariation accounted for by dimension-specific, non-shared environmental factors was in excess of any genetic influences. This raises the possibility that several unique biological and psychological factors may shape specific sexual problems reported by women. Other epidemiological studies show that factors such as anxiety, depression, relationship satisfaction, co-morbid physical conditions, age, and contextual factors (such as cultural expectations and situational norms) correlate with reports of FSD [4,30]. Our results should encourage further research into these unique etiological factors underlying specific FSD symptoms. Studies using MZ twins discordant for FSD symptoms could help identify the non-shared developmental pathways responsible for specific symptoms (or identify protective factors). Longitudinal genetic designs could help quantify phenotypic and heritable variation in FSD symptomatology in a prospective fashion while overcoming the limitations of current self-report measures, particularly when used in cross-sectional surveys. Prospective designs also afford
better estimates of measurement error so that heritability and environmental parameters can be estimated more precisely. Such designs could be used to identify environmental risk factors which influence “situational” or short-term dysfunction or specific sexual problems whereas genetic factors may influence long-term levels of sexual functioning.

Limitations
The present study had some methodological limitations. First, to allow analysis on a full dataset, missing data were imputed using the item-specific means of different age clusters. Missing data constitutes a loss of information that generally decreases the efficiency of parameter estimates and reduces the sensitivity of the statistical analysis. As most missing data techniques have been developed under the assumption of multivariate normality, we opted for mean value imputation to deal with our missing data. Although this procedure has been criticized in the past, some researchers argue that within-class mean value imputations can be used if carefully chosen and is only problematic in datasets where the proportion of non-response is high [39,40]. Given the low number of mean imputed data in the present study (72 individuals = 4.8% of the whole sample), it is unlikely that the standard errors of the items have been significantly underestimated and therefore resulted in significantly distorted item distribution. Furthermore, no significant differences in FSFI scores could be detected between women with full data and women with imputed data.

Approximately 70% of our sample were 50 years or older, which contrasts with some previous twin samples [22]. Thus the prevalence of FSD symptoms in the current sample may have been larger because it comprised more postmenopausal women who often report greater frequencies of sexual problems [41,42]. Indeed, our frequencies were comparable to rates of sexual symptoms reported by postmenopausal women [42]. The age-related effects on sexual function reported here and elsewhere indicate that caution must be exercised in generalizing the current findings to other age groups. Age-related effects in sexual functioning are of course interesting both in view of twin designs and clinical perspectives. Heritability of FSD could change over time and several mechanisms may explain potential age-related variability in heritability, such as changes in exposure to environmental risk/protective factors and active gene-environment associations (e.g., small genetic effects may become larger later in life as a result of genetic influences on choice of sexual partner or frequency of desire sexual activity). Second, our data may have been affected by reporting biases given the sexual nature of the measures, leading to some underestimation of FSD symptoms. This could be reflected in the finding that most of the variance and covariance was attributable to non-shared environments, which include measurement error. However, our response rate (50%) is comparable to other epidemiological-level sex surveys [22,43,44]. Moreover, our finding of large non-shared environmental influences on the FSD dimensions is consistent with previous evidence [22], and our measure of FSD has been demonstrated to show excellent validity and reliability [31]. Furthermore, others have reported that sexual behavior surveys tend to overestimate sexual liberalism, activity, and dysfunction but that this bias does not seriously compromise population estimates, as judged by the pattern of effect sizes. Finally, the findings should be interpreted with appropriate caution in view of general limitations of the twin method. Although our sample is representative of British singletons, our finding may not extrapolate to other populations. We did not provide a check against the equal environments assumption for MZ and DZ twins and so replicating our findings in other family designs (e.g., adoption studies) would be a suitable strategy.

Although the multi-dimensional FSFI is regarded as the gold-standard in self-report assessment of FSD, the instrument is limited in its capacity to measure more physiological aspects of sexual functioning as well as constructs such as “sexual quality of life.” Therefore, we would ideally have used additional instruments to capture the multidimensionality of subjective sexual well-being and physical functioning. Furthermore, no specific environmental factors were investigated in the context of this study although the results indicate a crucial role of non-shared environmental factors in explaining variation and co-variation of the various FSD dimensions. This, however, was beyond the scope of this study which aim was to quantify the underlying multivariate etiological structure of the FSD phenotype.

In conclusion, our results show FSD to be etiologically heterogeneous in terms of its underlying genetic and environmental factor structure. Specific sexual dimensions were found to be influenced by two common genetic factors as well as relatively dimension-specific non-shared environmental factors. These non-shared environmental
influences (which include measurement error) were by and large the most substantial effect on FSD symptoms. Our results, if replicated, indicate that FSD should be view as multidimensional from clinical, phenotypic and etiological perspectives. The deliberations around DSM-5 should, indeed, consider etiological subtypes of FSD. In the meantime, clinical researchers should work to identify dimension-specific predisposing or maintaining factors that could be targeted in treatment as well as using gene-mapping approaches to resolve the molecular basis of heritable factors.

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Statement of Authorship

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